The innate immune system is the first line of defense against pathogens. Some membrane and cytoplasmic receptors, present in each cell, are specialized in recognizing pathogen-related molecular patterns, such as viral nucleic acids or bacterial cell wall components. Their binding to these receptors activates signalling pathways that lead to the initiation of innate immune responses, changes in transcription patterns, production of signalling molecules - cytokines and interferons. Type I interferons induce the transcription of interferon-stimulated genes, including IFIT proteins (*Interferon-induced proteins with tetratricopeptide repeats*) and various other effectors that neutralize the threat. Proteins from the IFIT family are key antiviral proteins in vertebrates. They are known to bind viral RNA molecules and prevent the production of foreign proteins. IFITs are generally not produced in cells under basal conditions, but after immune stimulation they are very strongly expressed in all infected cells, reaching millions of copies of protein per cell. However, there are cells of the immune system, macrophages and lymphocytes, in which basal expression level of at least some IFIT proteins is maintained. These cells arrive as first at the site of the microbial invasion. Thus, we believe that IFIT proteins that are basally expressed in them, take part in the regulation of pro- and anti-inflammatory factors and keep these cells in constant readiness to trigger the body's immune defense mechanisms.

The goal of our project is to understand the role of IFIT proteins expressed in macrophages under basal conditions and regardless of immune stimulation. We are particularly interested in gaining knowledge about the role of IFIT proteins in the regulation of pro- and anti-inflammatory cytokines, maintaining the state of immune readiness for rapid cellular responses, as well as silencing inflammatory reactions after the threat has ceased, and returning of the cell to its basal condition. We will use a broad range of molecular and cell biology techniques, biochemistry and structural biology, in order to study the involvement of IFIT proteins (primarily IFIT2) in the RNA metabolism of immune response factors and IFIT2 impact on a number of important cellular processes such as protein biosynthesis, RNA transport and RNA degradation. We also intend to develop a tool compound based on the targeted degradation of IFIT2 protein that could become a drug with potential anti-inflammatory and antiviral properties. Drugs counteracting the overproduction of cytokines can be useful in prevention of the “cytokine storm”, which for example is the cause of acute lung injury in COVID-19 and respiratory failure in SARS-CoV-2 infected patients.

The obtained results will broaden our knowledge about molecular recognition in general, and mechanisms of protein-RNA interactions in the immune response. We intend to discover new, yet unknown functions of IFIT proteins and describe new mechanisms of gene expression regulation. We believe that the results obtained in this project will help to better understand the basics of immune response in cells responsible for the first contact with pathogens. In the longer term, the results may also be helpful for better understanding of the causes of autoimmune diseases, in immuno-oncotherapy or development of mRNA vaccines, as well as treatment or prevention of acute inflammation resulting from the cytokine storm.